EUROPEAN AGENCY FOR THE EVALUATION OF MEDICINAL PRODUCTS (EMEA)

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INTRODUCTION

History of the European Union

After the Second World War, the idea of a "United States of Europe" was promulgated and in 1957, the Treaty of Rome was signed instituting the European Economic Community (EEC) between six countries (Germany, Belgium, France, Italy, Luxembourg, and the Netherlands). In 1973, Ireland, the United Kingdom, (UK) and Denmark joined the EEC. In 1974, heads of state and government decided that a European Parliament should be elected by direct universal suffrage and that it would meet regularly as the European Council (EC) to deal with community affairs and political cooperation. Greece acceded to the EC in 1981, and Spain and Portugal joined in 1986. In 1992, the 12 Foreign Affairs Ministers signed the Maastricht Treaty instituting the European Union (EU), which also included the four freedoms of labor, capital, goods, and services. Finally, Austria, Finland, and Sweden joined the EU in 1995. The Treaty of Amsterdam, which entered into force on May 1, 1999, made further institutional changes such that no draft text can become law without the formal agreement of both the European Parliament and the Council. Thus, the EU now consists of 15 member states, each of which has its own national government and legislative bodies.

The EEC has three important powers:

1. It adopts "European laws" that apply in the 15 countries ("directives" and "regulations").
2. It disposes of a budget to finance certain programs carried out in its member states.
3. It signs international agreements on cooperation or trade.

All these decisions are taken by common institutions sitting in Brussels, Strasbourg, and Luxembourg. Since 1974, the EC has brought together heads of state and government of the 15 member states, as well as the the president of the Commission, to set key guidelines and political goals and to arbitrate on questions for which agreement has not been found within the EU Council of Ministers. Each member country presides over the Council for a six-month period.

EUROPEAN UNION INSTITUTIONS AND LEGISLATIVE INSTRUMENTS

The European Commission, representing the Community's interests, draws up common projects and, after a decision has been taken by the EU Council of Ministers, sees that they are properly implemented. It is directed by 20 commissioners and is assisted in its work by a permanent staff of 17,000, most of who are based in Brussels. It is independent of the governments but is subject to control of the European Parliament. It implements common policies and negotiates international agreements. It may bring an action before the European Court of Justice should Community laws not be respected by the member states. It is here, within the Pharmaceuticals and Cosmetics Unit of the Directorate-General for Enterprise (formerly the Directorate-General for Industry, DG III), that European legislation on medicines is drawn up and implemented.

The European Parliament is made up of 626 deputies who are elected by direct universal suffrage every 5 years. It examines all proposals for European directives and regulations, which it may accept, modify, or refuse. It supervises the work of the European Commission, which it can dismiss with a motion of censure, and it votes the annual Community budget.

The EU Council of Ministers meets in order to adopt proposed European directives and regulations in light of the advice given by the European Parliament. The ministers convene depending on the subject that the Council is dealing with and according to their areas of competency (i.e., the ministers of health of the 15 member states are present for a Council dealing with questions of drug regulation or health.) The country presiding over the EC holds the presidency of the EU Council of Ministers. Due to the principle of subsidiarity, Community legislation is only introduced on points of common interest and in order to further the aim of a balanced and dynamic Europe.

The Council of Ministers can adopt several types of legislation, which are more or less restrictive:

"Regulations" are binding and directly applicable to all citizens.
"Directives" are binding on all citizens but indirectly (i.e., after they have been "transposed" into the laws of each country).
"Decisions" are binding and directly applicable but only to the institutions, bodies, businesses, or citizens specifically named.
"Recommendations," "advisory opinions," and "resolutions" are consultative or guidance texts addressed to the states.

EU LEGISLATION FOR PHARMACEUTICAL AND VETERINARY PRODUCTS

The foundation of European pharmaceutical legislation is Directive 65/65/EEC (1), which when promulgated in 1965, applied only to the initial six member states. In this directive, the definition of a medicinal product is given and the data required to obtain approval is described. This original directive is continually updated, amended, and supplemented with subsequent legislation, but remains the basis of pharmaceutical legislation.

Ten years following the first direction, three new directives sought to further promote public health and the free movement of medicinal products within the community. Directive 75/318/EEC (2) set analytical, pharmaco-toxicological, and clinical standards for testing proprietary medicinal products. Directive 75/319/EEC (3) established the Committee for Proprietary Medicinal Products (CPMP) and its partial mutual recognition procedure, while Directive 75/320/EEC (4) set up a Pharmaceutical Committee to examine problems in implementing the pharmaceutical directives.

In the years that followed, cooperation between national health authorities at EU level was further encouraged. Two Directives, 83/570/EEC (5) and 87/22/EEC (6), set up the Multistate procedure and the Concertation procedure. These procedures provided a mechanism for exchange of information on all aspects of product licensing between member states and made it easier for national licensing authorities to recognize each other's decisions. In the Concertation procedure, the CPMP was charged with forming an opinion on the feasibility of an application, which, however, was not binding on the member states' national authorities. The Multistate procedure was based on the principle of recognition of an approval in one member state by the national health authorities in other member states.

The European Agency for the Evaluation of Medicinal Products (EMEA) was established by Council Regulation (EEC) No 2309/93 (7) of July 22, 1993, with London chosen as its seat by decision of the Council on October 29, 1993. It began operation on February 1, 1995. Regulation 2309/93 also established the legal basis for a single community-wide centralized procedure for the approval of medicinal and veterinary products.

Simultaneously, Directive 93/39/EEC (8) amended Directives 65/65/EEC (1), 75/318/EEC (2), and 75/319/EEC (3) and established the Decentralized Procedure (commonly known as the Mutual Recognition Procedure).

THE EMEA

Mission

The Mission of the EMEA is to contribute to the protection and promotion of public and animal health by:

Mobilizing scientific resources from throughout the EU to provide high quality evaluation of medicinal products, to advise on research and development programs, and to provide useful and clear information to users and health professionals

Developing efficient and transparent procedures to allow timely access by users to innovative medicines through a single European marketing authorization

Controlling the safety of medicines for humans and animals, in particular through a pharmacovigilance network and the establishment of safe limits for residues in food-producing animals

Structure

The European system is based on cooperation between the national health authorities of the member states and the EMEA. The EMEA acts as a focal point of a network that coordinates the scientific resources made available by the member states. This partnership between the EMEA, national health authorities, and the EU institutions is crucial to the functioning of the European authorization procedures.

A Management Board supervises the EMEA, while its scientific activities are largely carried out through its two scientific committees and their working parties. The Board, scientific committees, and their working parties are supported by the EMEA secretariat, headed by an Executive Director.

The Management Board is made up of two representatives from each member state, from the European Parliament and from the European Commission. Representatives of Iceland and Norway, who are members of the European Economic Area (EEA) but not of the EU, also attend meetings of the Board. As of January 1, 2000, these countries formally joined the EMEA. The Management Board appoints the Executive Director, and approves the budget and work program each year. On the recommendation of the European Parliament, it gives discharge to the Executive Director for the implementation of the budget.

The principal scientific bodies of the EMEA are the CPMP and the Committee for Veterinary Medicinal Products (CVMP). They are made up of two members from each member state as well as from Norway and Iceland, and are appointed to give independent scientific advice to the EMEA. The EMEA Secretariat comprises four units: administration, evaluation of medicines for human use, technical coordination, and evaluation of medicines for veterinary use.

The Administration Unit is responsible for carrying out administrative and financial functions to ensure that the Secretariat and staff are able to perform their statutory tasks under satisfactory conditions and thus, has two subsections for personnel, budget and facilities, and for accounting.

The Unit for the Evaluation of Medicines for Human Use is responsible for the following:

- management and follow-up of marketing authorization applications under the centralized procedure;
- postmarketing maintenance of authorized medicinal products;
- management of community referrals and arbitrations arising from the mutual recognition procedure; and
- provision of support to European and international harmonization activities of the CPMP and its working parties.

This unit consists of three subdivisions or sectors: for regulatory affairs and pharmacovigilance, for biotechnology and biologicals, and for new chemical substances.

The Unit for the Evaluation of Medicines for Veterinary Use is responsible for the following:

- management and follow-up of marketing authorization applications under the centralized procedure;
- management of applications for the establishment of maximum limits for residues of veterinary medicinal products that may be permitted in foodstuffs of animal origin;
- postmarketing maintenance of authorized medicinal products;
- management of community referrals and arbitrations arising from the mutual recognition procedure; and
- provision of support to European and international harmonization activities of the CVMP and its working parties.

It has two sectors: for CVMP and veterinary procedures, and for safety of veterinary medicines.

The Technical Coordination Unit is responsible for providing logistical support to both human and veterinary medicine evaluation activities as well as a number of general services to the EMEA, including document management, conference services, and information technology support. It has four sectors: for inspections, for document management and publishing, for conference services, and for information technology. The sector for inspections coordinates the work of inspectors, the implementation of mutual recognition agreements, and the monitoring of medicines authorized in the community. It provides the secretariat of the Quality Working Party and coordinates the Agency's quality management program.

EMEA Scientific Committees

The CPMP and the CVMP are the scientific committees set up to facilitate the adoption of scientific decisions between member states on the authorization of medicinal products on the scientific criteria of quality, safety, and efficacy.

When working for the EMEA, members of the CPMP and CVMP act independently of their nominating member state. The scientific committees are aided by a network of approximately 2300 European experts, nominated by the national competent authorities of the member states on the basis of proven experience in the assessment of medicinal products. Experts may serve on working parties or expert groups of the CPMP or CVMP.

The scientific committee decides the appointment of rapporteurs and corapporteurs, i.e., those members of the CPMP or CVMP who take the lead in reviewing a dossier. The committees are required to ensure that all members undertake the role of rapporteur or corapporteur. Compensation is provided to national competent authorities for the services provided by committee members or European experts at the specific request of the agency.

THE CPMP AND THE EVALUATION OF MEDICINAL PRODUCTS FOR HUMAN USE

A CPMP member acts as rapporteur or corapporteur for centralized procedures and the CPMP gives an official

opinion on whether an application for marketing is approvable or not. The EMEA is intimately involved in the management of this procedure up to the issue of the marketing authorization. The EMEA's involvement also includes preparation of the CPMP opinion in all 11 official EU languages. Quality management standards have been implemented for the preparation of scientific advice and opinions, and a tracking system throughout the life cycle of centrally authorized products has been developed. Postauthorization, variations, and extensions to the license may be submitted and rapporteurs play a major role with these maintenance activities. There is also ongoing activity with regard to adverse drug reaction (ADR) reporting, periodic safety update reports (PSURs), and other follow-up measures. Rapporteurs and corapporteurs are particularly involved in urgent safety restriction procedures.

Pharmaceutical sponsors may seek advice on their development programs from the CPMP. The CPMP has set up a scientific advice review group to strengthen and widen CPMP input and to guarantee the availability of proper expertise. A standard operating procedure for the giving of scientific advice by the CPMP for innovator medicinal products has been adopted.

Working Parties

The CPMP and CVMP each have four working parties, as well as a joint CPMP/CVMP Quality Working Party. There is also an EMEA working party on Herbal Medicinal Products.

The CPMP working parties are concerned with biotechnology, efficacy, safety, and pharmacovigilance. The CVMP working parties are concerned with safety of residues, immunological veterinary products, veterinary pharmacovigilance, and efficacy.

These working parties produce position papers, points to consider, notes for guidance, and joint CPMP/CVMP/International Conference on Harmonization (ICH) Guidelines that provide up-to-date scientific opinions on matters of current interest to all member states and pharmaceutical and veterinary manufacturers.

Biotechnology working party

This working party considers aspects of the manufacture and control of biotechnological and biological medicinal products and is also involved in the provision of scientific advice. For example, workshops were held recently on the application of assays for markers of transmissible spongiform encephalopathies (TSE) and on the potential risk of transmitting new variant Creutzfeld–Jakob Disease (nv-CJD) through plasma-derived medicinal products.

Efficacy working party

Clinical trial methodology and guidelines for special disease-related therapeutic fields are discussed in this party. In cooperation with other working parties, guidance on modified release oral and transdermal dosage forms, on pharmacokinetics, and on clinical investigation of new vaccines, gene therapy, and cell-cultured influenza vaccines has been given.

Pharmacovigilance working party

This working party considers safety-related issues at the request of both the CPMP and national authorities, resulting in the harmonization of the summary of product characteristics and package leaflets of marketed products. Regular video conferences are held with the U.S. Food and Drug Administration (U.S. FDA) to discuss issues of mutual interest. A pilot project was started for the electronic transmission of individual case safety reports with a restricted number of participants from national authorities and marketing authorization holders.

Safety working party

Preclinical and safety issues are discussed, and in cooperation with the Biotechnology Working Party, a note for guidance on the quality, preclinical, and clinical aspects of gene transfer products was produced recently.

Ad hoc and other groups

Ad hoc groups on excipients, Lipodystrophy, and antiretroviral medicinal products have been formed. A multidisciplinary group has been set up to evaluate medicinal products containing thiomersal with a view to limiting exposure to mercury and organomercurial compounds.

Cooperation with Competent Authorities

European Monitoring Centre for Drugs and Drug Addiction (EMCDDA)

The EMEA has supported the development of guidelines on risk assessment of new synthetic drugs.

International Conference on Harmonization (ICH and VICH)

The EMEA, as one of the six partners in the ICH process, is intimately involved in production and update of ICH guidelines. The Unit for the Evaluation of Medicinal Products for Human Use supports the Steering Committee, the EU topic leaders, the CPMP, and the various working parties in the preparation, review, and administration of ICH guidelines. Similarly, since establishment of the VICH

in 1996, the Unit for Evaluation of Veterinary Medicinal Products supports the Steering Committee and the CVMP as well as the various working parties in this initiative.

Central and Eastern Europe

Many central and eastern European countries (CEEC) are candidates for accession to the EU. The candidates are Bulgaria, Czech Republic, Estonia, Hungary, Latvia, Lithuania, Poland, Romania, Slovakia, Slovenia, and Cyprus. In order to help pharmaceutical registration authorities in these countries prepare for EU membership, a Collaborative Agreement of Drug Regulatory Authorities of European Union Associated Countries (CADREAC) was formed. In addition to this agreement, a simplified procedure for the recognition of centrally authorized medicinal products by the national authorities of CEEC was established. The procedure is optional and is initiated at the request of the marketing authorization holder in the EU.

In addition, under the auspices of a pharmaceutical Pan-European Regulatory Forum (PERF) set up by the European Commission, the EMEA administers and provides executive assistance to CEEC and EU regulators in the conduct of working groups and training sessions in order to facilitate the adoption of common technical requirements. Topics include the implementation of Community legislation, pharmacovigilance, and the assessment of dossiers for marketing authorization for quality safety and efficacy.

Meanwhile, to help eliminate technical barriers to pharmaceutical trade with the CEECs, protocols to permit mutual recognition of good manufacturing practice compliance for medicinal products are being negotiated.

THE CVMP AND THE EVALUATION OF MEDICINAL PRODUCTS FOR VETERINARY USE

The CVMP operates in a similar fashion to the CPMP and is heavily involved in the review of centralized procedures for veterinary products. The CVMP has developed a broad range of new guidelines to assist applicants on topics related to research and development and for which no guidance existed previously.

The Unit for the Evaluation of Medicinal Products for Veterinary Use has also been involved in the PERF initiative as well as other activities related to implementation of Community legislation and the quality of medicinal products.

When the EMEA opened in January 1995, more than 600 "old" substances remained for which maximum residue limits (MRLs) had to be established. The assessment of these products was completed before the January 2000 deadline.

Veterinary Working Parties

Similarly to the CPMP Working Parties, the Efficacy, Safety of Residues, Immunologicals, and Pharmacovigilance Working Parties develop guidelines for the testing and reporting requirements of studies for products for veterinary use.

INSTITUTIONAL PARTNERS

The major contact within the services of the European Commission is the Pharmaceuticals and Cosmetics Unit of the Directorate-General for Enterprise; however, there is also continued exchange of information with the Directorate-General for Health and Consumer Protection. Other contacts include the Directorate-General for Research and the Joint Research Center.

European Technical Office for Medicinal Products (ETOMEP)

The European Commission Joint Research Center has established a technical office at the EMEA responsible for the management of a telecommunications network and other computer technologies to facilitate the dissemination of information on medicinal products. It also manages the EMEA Internet website. A new mechanism for the secure exchange of documents through the Internet has been put in place to facilitate, among other things, the transmission of individual case safety reports within the pilot project on pharmacovigilance between EMEA, national authorities, and the pharmaceutical industry.

The European Union drug regulatory authorities' network (EudraNet) is an internetworking service provided to EU medicinal regulatory authorities in collaboration with the European Commission Directorate-General for Industry. Part of the EudraNet is accessible to industry and the general public.

Joint Interpreting and Conference Service (JICS)

The JICS of the European Commission serves the institutions of the EU, as well as the decentralized agencies and bodies located in EU member states. A representative of the JICS is based at the EMEA to coordinate translation and conference needs. A glossary of specialized and technical EMEA terms to assist interpreters at EMEA meetings is being developed.

The European Department for the Quality of Medicines (EDQM)

European Pharmacopoeia (EP)

The EP was founded by Belgium, France, Germany, Italy, Luxembourg, Netherlands, Switzerland, and the United Kingdom in 1964, under a Council of Europe Convention, to help standardize their national pharmacopoeias. The EP now has 26 signatories (15 member states, the European community, and 10 other European countries). Its monographs have force of law, replacing the old national pharmacopoeias. Directive 75/318/EEC requires EU pharmaceutical manufacturers to use these monographs when compiling marketing authorization applications. The EMEA participates in the work of the EP Commission as part of the EU delegation.

European Network of Official Medicines Control Laboratories (OMCL)

This is a joint project between the EU and the Council of Europe to allow the coordination of laboratory controls between the EU and EFTA members. In 1999, a contract was signed between the EMEA and the EDQM to organize sampling and testing of centrally authorized medicinal products by the OMCL network.

EUROPEAN APPROVAL PROCEDURES

There are two European procedures for obtaining a marketing authorization in more than one country belonging to the EU. These are the Centralized Procedure and the Decentralized or Mutual Recognition Procedure.

Centralized Procedure

The Centralized Procedure must be used for biotechnology products and can be used for so-called high technology products as well as for new active pharmaceutical ingredients (i.e., products that have never before been approved for marketing). The Centralized Procedure is laid down in Council Regulation (EEC) N° 2309/93 (7) and Directive 93/41/EEC (9).

In the Centralized Procedure, one license to market the drug in the entire EU is issued and in principle there is only one evaluation of the dossier. In fact, both a rapporteur and corapporteur are appointed, and each assesses the dossier with its own team. The rapporteur and corapporteur are members of the CPMP who are assigned to a particular dossier by the CPMP. Each member is obliged to act as rapporteur or corapporteur.

Before submission of the dossier, the Sponsor Company contacts the CPMP or CVMP to announce its intention to make a registration submission and to request appointment of a rapporteur. If, as is usually the case, the Sponsor has had contact with national health authorities, it may request that a particular CPMP or CVMP member be appointed as rapporteur. The CPMP/CVMP is not obliged to follow this request, but in many cases either the rapporteur or the corapporteur is the CPMP/CVMP member requested.

After submission, the rapporteur and corapporteur have 120 days to perform their review and to write a draft assessment report. The two assessments are then discussed by the parties and a list of outstanding issues is sent to the sponsor, at which point the clock is stopped. When the answers have been received, the rapporteur has another 30 days to finalize the assessment report, which is sent to the CPMP or CVMP. CPMP/CVMP members also receive a copy of Part I of the dossier and may request the full dossier. After a total of 210 days, the CPMP or CVMP delivers an opinion: favorable or unfavorable.

If the opinion is favorable, the second stage of the procedure, the decision-making process, begins. During the decision-making process, the Commission Services check that the marketing authorization complies with community law and turn the agency opinion into a binding decision for all the member states. Should the CPMP decision be unfavorable, the sponsor may appeal and a second CPMP opinion must be prepared within 60 days.

The agency sends the Pharmaceutical Unit of the Commission its opinion in all 11 community languages together with the Summary of Product Characteristics (SPC), the particulars of the manufacturing authorization holder responsible for batch release and of the manufacturer of the active substance, as well as the labeling and package leaflet. The commission has 30 days to prepare a draft decision. During this period, various commission directorates-general are consulted and are able to give their opinions.

The draft decision is then sent to the Standing Committee on Medicinal Products or the Standing Committee on Veterinary Products for their opinions. Should there be detailed opposition from a member state to the draft commission decision, the standing committee can refer it back to the CPMP if the opposition is scientific. If the matter is nonscientific, a vote is taken and the council decision is made on the basis of a qualified majority. Each member state has a different number of votes depending on size and importance, and the majority of votes must be in favor. If there is no opposition within 30 days, the draft decision is forwarded to the Commission

Secretariat-General for adoption, enabling the Commissioner for Enterprise and the Information Society to issue the final decision. The final decision is published in the Official Journal of the European Communities.

Decentralized Procedure

The Decentralized Procedure is made on the basis of mutual recognition. Council Directive 93/39/EEC (8) has been implemented in all member states in accordance with Directives 65/65/EEC (1) and 75/319/EEC (3). The sponsor makes a submission to the national health authority of one member state, with a request to assess the dossier for mutual recognition. Within 210 days, the so-called Reference Member State (RMS) must approve the application, prepare an assessment report, and agree on an SPC. The clock may be stopped to obtain further information during this time.

The mutual recognition submission can then be made to any number of the other member states, and the RMS sends a copy of the assessment report to the concerned member states (CMS). Within 90 days, member states must raise serious objections and if there are none, each CMS issues a national marketing authorization with an identical SPC.

To facilitate the mutual recognition procedure, a Mutual Recognition Facilitation Group (MRFG) and a Veterinary Mutual Recognition Facilitation Group have been set up, although this was not foreseen in the original directive. These groups meet one day before each CPMP/CVMP meeting. The objections raised are discussed within the group and the RMS tries to reach agreement on the approval possibilities of the dossier and the most appropriate labeling. If necessary, breakout sessions with the sponsor can be held to finalize labeling details.

Should no agreement be reached within the MRFG/VMRFG, the matter is sent to the CPMP/CVMP for an opinion. Thereafter, the procedure is similar to that during the centralized procedure—the end result being a commission decision after which national licenses must be issued within 30 days.

Referrals and Arbitration

A sponsor company or a national authority may make referrals to the EMEA under Article 10 of Directive 75/319/EEC, in order to harmonize the summary of product characteristics in all member states for products previously approved under national legislation.

Similarly, where there are public health concerns as a result of pharmacovigilance data, nationally authorized products or products authorized by the mutual recognition procedure may be referred under Articles 12 or 15 of Directive 75/319/EEC. The CPMP/CVMP gives an opinion on variation, suspension, or withdrawal of the marketing authorization in such cases.

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